PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IN 02/00245	International filing date *(day/month/year)* 26.12.2002	Priority date *(day/month/year)* 26.12.2002
International Patent Classification (IPC) or both national classification and IPC C07C305/00		
Applicant LUPIN LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.04.2004	10.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer English, R Telephone No. +31 70 340-2860

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 02/00245

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-33 as originally filed

Claims, Numbers

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: US 6 458 949 B1 (V.K. Handa, et al.) 1 October 2002
D2: EP 0 791 597 A (Lupin Laboratories) 27 August 1997

1. **Subject-matter**

The present application concerns a three-step process for the preparation of certain cephalosporin derivatives of formula (II):

step 1: the preparation of compounds of formula (I) by reaction of 4-halo-2-oxyimino-3-oxobutyric acid derivatives of formula (IV^1) with the adduct (VII) of dimethylformamide (DMF) with sulphuryl chloride,

step 2: the preparation of compounds of formula (VIII) by reaction of compounds of formula (I) with compounds of formula (V), and

step 3: the preparation of compounds of formula (II) by reaction of compounds of formula (VIII) with thiourea.

The intermediates in this process of formula (I) are also claimed *per se*.

2. **Obvious error**

It would appear that an error has been made throughout the present application. It is obvious that the reaction of a carboxylic acid of formula (IV^1) with a chlorosulphate ester of formula (VII) would not lead to an acyl sulphonate of formula (I) as indicated throughout the present application. Instead an anhydride of the carboxylic acid and the sulphate ester from which the chlorosulphate is derived can be the only product of the reaction (see also D2, reaction scheme C on page 17 where a similar reaction is carried out).

Consequently, the International Preliminary Examination Authority considers that

there is an obvious error in the present application (Rule 91.1 PCT), namely that an oxygen atom has been omitted from formula (I) at every occurrence and that formula (I) should read X-CH_2-CO-CNOR-CO-**O**-SO_2-O-CH=$N^{(+)}$Me2 $Cl^{(-)}$. This correction appears to be allowable under Rule 91.1 PCT.

The remainder of the present International Preliminary Examination Report assumes that this correction has been made.

4. **Novelty**

Document D1 (example 1) describes a process for the preparation of compounds corresponding to a compound of formula (II) of the present application in which R is methyl, R_1 and R_2 are hydrogen and R_4 is 2-furoylthio. In this process 4-bromo-2-methoxyimino-3-oxobutyric acid is converted to the corresponding acid chloride and then reacted with silylated 7-amino-3-(2-furoylthiomethyl)-3-cephem-4- carboxylic acid to produce the bromo cephalosporin derivative which is cyclised with thiourea to form the thiazolyl cephalosporin derivative.

This process differs from the process of the present invention in that the activated derivative used is the acid chloride of the compound of formula (IV^1) in place of the asymmetrical anhydride of formula (I) formed with the adduct of DMF and sulphuryl chloride (formula (VII)). The compounds of formula (I) do not appear anywhere in the prior art. Consequently, the subject-matter of claims 1-15 appears to be novel and to satisfy the requirements of Article 33(2) PCT.

5. **Inventive step**

The document D1 is regarded as being the closest prior art to the subject-matter of claims 1,2,5 and discloses a process for the preparation of compounds corresponding to those of formula (II) of the present application (see paragraph 4 above). The subject-matter of claims 1,2,5 differs from this known process in that it uses the adduct of DMF and sulphuryl chloride to activate the carboxylic acid in the reaction with the amine group of the cephalosporin derivative of formula (V) in place of the acid chloride in the prior art. The yield of the process when applied to the synthesis of ceftiofur is stated to be 21.4% in the present application (example 5), though it is not clear which part of the preparative process the quoted yield refers to, since 1.65 g of ceftiofur is 3.15 mmol or 1.3 % yield based on 235.2 mmol of furaca.

This yield compares to 59.3% in D1 (65.9 x 90 % in example 1) including the initial silylation of furaca. Clearly an enhanced yield is not the technical effect of the use of the adduct of DMF and sulphuryl chloride to activate the acid in the formation of the amides of formula (VIII). No other technical effect can be determined from the information given in the present application.

The problem to be solved by the present application may therefore be regarded as the provision of an alternative method for the preparation of compounds of formula (II). The applicant solves this problem by means of the activated intermediates of formula (I) in the three-step process as outlined in paragraph 1 above.

Document D2 describes (page 17, scheme C) a process for the preparation of the same cephalosporin derivatives. In this process 1.1 equivalents (e.g. example 1A) of 2-(2-aminothiazoyl)-2-methoxy-iminoacetic acid (formula III in D2) is reacted in dichloromethane with the adduct formed from the reaction of DMF and sulphuryl chloride to form the corresponding activated derivative in 82.5 % yield. In example 1, 1.08 equivalents of this derivative are then reacted with a silylated cephalosporin derivative similar to those of formula (V) in dichloromethane at -55 °C in the presence of dimethylaniline of the present application to give the corresponding amide derivatives.

The person skilled in the art would expect that replacement of 2-(2-amino-thiazoyl)-2-methoxyiminoacetic acid with the 4-halo-2-oxyimino-3-oxobutyric acid derivatives of formula (IV^1) of the present application in the prior art process of D2 would lead to the cephalosporin derivatives of formula (VIII) which can then be converted to the final cephalosporin derivatives of formula (II) by the known process (see D1, example 1, stage II).

At least one of the features in each of the dependent claims 3,4,6-15 is present in D1 or D2. Consequently, the subject-matter of present claims 1-15 cannot be considered to involve an inventive step (Article 33(4) PCT).